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10/812,764	03/30/2004	Choong-Chin Liew	4231/2055J	4511

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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/812,764	LIEW, CHOONG-CHIN	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/11/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of Group I, further electing the marker CLK1 in the reply filed on 1/26/07 is acknowledged. Claims 49-57 are pending and examined in this office action.

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 49-57 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 17-35 of copending Application No. 10/980850. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application recite methods for diagnosing or prognosing liver cancer by determining the level of RNA transcripts expressed in blood from one or more biomarkers of Table 1 or Table 2, comparing to individuals not having liver cancer or having liver cancer, wherein differential expression or the same expression indicates the

presence of liver cancer. Though the claims do not particularly require CLK1, CLK1 is one of the genes listed in Table 1. It would have been prima facie obvious to one of ordinary skill in the art to practice the claimed invention in the 10/980850 application with any or all of the genes recited in the claims, including CLK1. One would have been motivated by the express suggestion in the claims to use one or more of the biomarkers of Table 1.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 49-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) The claims are all confusing because the preamble of claim 49 recites that the method is for detecting liver cancer, yet the last line of the claim recites that the comparison is "indicative of coronary artery disease." It is not clear from the claims, therefore, how the claimed method accomplishes the stated goal of detecting liver cancer in a human test subject. It appears that the recitation of coronary artery disease is an editing error since the rest of the claims and the response filed 1/26/07 refer to liver cancer and not coronary artery disease. The remaining

analysis in this office action is given as if the claim did recite liver cancer in the final line, in the interest of compact prosecution.

(B) The recitation "unfractionated samples of lysed blood" in claim 51 is unclear in light of the prosecution history in this application and in the parent applications from which this application claims priority. Claims 51-57 depend from claim 51 and are indefinite for this same recitation. The specification does not define what is meant by an "unfractionated samples of lysed blood." On its face, such a limitation appears to mean that the lysed blood sample is not separated into constituent parts, however, interpretation of the claim in light of the specification, pending claims, and applicant's remarks filed with the amendment results in ambiguity with regard to the meaning of this claim limitation.

An example in the specification which discusses lysis prior to quantification includes a centrifugation step after which the "pellet" is further treated. This is a fractionation after lysis but before quantification.

One might interpret detecting in "unfractionated sample of lysed blood" as requiring that the detection occur relative to RNA that was extracted from the entire blood sample without any prior separation into parts, which could be accomplished by direct extraction of the lysed blood without separating removing the plasma from the blood sample, for example.

Applicant set forth still a different definition for a similar claim limitation in the remarks filed introducing a similar phrase into the claims in the parent application 10/268730. In discussing basis in the specification for the limitation, applicant stated that the limitation refers to "a sample of whole blood which has not been fractionated into cell populations and includes a drop of blood (see remarks dated 4/25/05, at page 5)." This definition for unfractionated sample

of whole blood set forth by applicant would, therefore, allow a fractionation of the cellular material prior to RNA extraction (as exemplified in the instant specification in Example 5).

And so it is unclear what the metes and bounds of the phrase "unfractionated sample of lysed blood" actually encompasses in light of the lack of definition of the phrase in the specification and the many, conflicting possible interpretations in light of the specification, pending claims, and remarks by applicant.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 51-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The limitation "unfractionated samples of lysed blood" appears to be new matter. The amendment which added this limitation did not cite support for the limitation. The specification teaches at page 43 treating a sample with lysing buffer, centrifuging the sample, and then processing the pellet with RT-PCR (Example 5). Thus, the sample was fractionated prior to quantifying. The examiner was not able to identify basis for this limitation in the specification.

8. Claims 49-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention

The invention is drawn to a method detecting liver cancer in a human test subject. The claims all include a step of determining the level RNA encoded by the gene CDC-like kinase 1 (CLK1) in a blood sample obtained from said human and comparing the level with the level of control RNA encoded by said gene in RNA of blood samples from control subjects, and wherein said comparison is indicative of liver cancer in said human test subject. Thus, the independent claim, as written, states that a comparison of a human test subject CLK1 RNA level in a blood sample to control samples indicates that liver cancer is present in the test subject. The nature of the invention requires the knowledge of a reliable association between comparing CLK1 expression and the indication that liver cancer is present in a human. Further, the practice of the invention requires an understanding of how the presence of liver cancer effects the level of CLK1 expression in human blood in patients having liver cancer versus patients that do not have liver cancer but may have some other disorders.

Scope of the claims

The claims are extremely broad because they require set forth that any or all comparison between a test subject and RNA level from "control subjects" is indicative of disease. The claims are broad with regard to whether or not the comparison requires identifying a difference in expression or not, and if a difference is detected whether that is an increase in RNA levels or a

decrease in RNA levels. The claims are broad with regard to the "control subjects" would could encompass patients with liver cancer, healthy patients, patients with some other disease, such as hypertension, obesity, hyperlipidemia or rheumatoid arthritis, and set forth that the comparison alone is sufficient to indicate liver cancer, no matter the result of the comparison. Later claims further define the control subject and require a statistically significant difference or similarity in RNA levels between control subjects and test subject, but even these claims do not set forth the direction of the difference necessary to indicate liver cancer. The claims are very broad in scope because they encompass that ANY level and direction of difference in gene expression between the tested subjects is indicative of disease. That is, the claims do not set forth that one level should be higher or lower than the other, and further do not set forth how much of a "difference" between two individuals would be necessary to draw the conclusions set forth in the claims.

Teachings in the Specification/Examples

Regarding liver cancer, the specification provides example 26 wherein gene expression profiles of blood samples from individuals having liver cancer were compared with normal individuals, that is healthy patients. The specification teaches that 1,475 genes were identified as being differentially expressed, and regarding the instant claims, table 3X provides a list of these genes (Example 26). CLK1 is among the genes.

Table 3X teaches that the ratio of expression in patients with liver cancer samples relative to control samples is 0.61, indicating that in the tested samples, CLK1 was expressed, on average at a 0.61 times less level in patients with liver cancer versus healthy controls. The specification teaches that the samples included four patients with Liver cancer and three "control" individuals. Table 3Y teaches that this result is significant p=0.0001786.

The specification also teaches that CLK1 is differentially expressed ($p<0.05$) in the blood of patients having hypertension, obesity, hyperlipidemia and rheumatoid arthritis versus normal controls (tables 3A, 3B, 3E, 3H, and 3M). For each of these diseases, the specification is silent as to the nature of the differential expression. The specification fails to teach whether the difference is an up regulation or down regulation and the specification fails to teach the magnitude of the difference.

The claims suggest that detecting and comparing expression of CLK1 in a test patient versus any possible set of control patients alone is sufficient to indicate the presence of liver cancer (that is detect liver cancer). The plain language of the claims suggests that any comparison between a test subject and control subjects, even as few as two control subjects, is sufficient to conclude that liver cancer is detected.

The specification does not provide data to support the assertion in the claims- namely that comparison of the CLK1 expression level in a test sample to control subjects (any control subjects) is sufficient to conclude that liver cancer is present a test patient. Claim 54 is limited to a case where the control subjects do not have liver cancer, but they could still have any other possible disease or condition. For example, the claims are inclusive of control subjects that have hypertension or obesity. For this embodiment of the claims, the specification does not provide information about an essential aspect of the invention, namely, evidence that there is a difference in expression of the CLK1 gene between these two populations.

Furthermore, though the specification teaches that this gene is differentially expressed in liver cancer patients versus healthy patients, the specification teaches this is true for thousands of genes. There is no guidance or analysis of data in the specification to suggest that this gene in

particular is sufficient to conclude that liver cancer is present in a sample, as is instantly claimed. To the contrary, the specification clearly indicates that CLK1 is differentially expressed in test versus control patients for a variety of conditions.

State of the Prior Art and Level of Unpredictability

Observing differences in expression between two populations is a highly unpredictable endeavor. While the instant specification teaches that CLK1 is differentially expressed in a population of liver cancer patients versus control subjects, the specification does not establish that any particular level of expression of CLK1 (relative level or raw level) is sufficient to DETECT liver cancer to the exclusion of other disorders, which is encompassed by the instant claims, and indeed, suggested by the instant claims.

The expression of genes in example 26 was tested by hybridization of samples to a microarray that contains genetic information for tens of thousands of genes. This technology area is highly unpredictable, and as a result significant guidance is required to practice inventions data obtained from such experiments. Lee (Clinical Chemistry, 47:8, 1350-1352 (2001)) teaches that despite the technical accuracy of individual observations on an array, these data "are much more prone to numerous false-positive findings fundamentally because of (a) an extremely large number of observations and (b) a very wide dynamic range of gene expression values obtained from gene chip experiments." In view of these unpredictable aspects of applying such data, Lee teaches that replication is necessary to begin to screen out false positive results. There is no replication in the instant specification.

Chenchik et al. characterize CLK1 as a gene that is a "stress gene" meaning that it modulates cellular response to stressors (¶0019 and Example 2). Thus differential expression of

this gene in the blood of patients may simply indicate stress in the patient. This exemplifies that it is highly unpredictable whether or not one can conclude, simply from a blood sample of a test patient, that liver cancer is present, since differential expression versus a control could indicate some other disorder or phenotype is present, whether that is obesity, hypertension, rheumatoid arthritis, hyperlipidemia, some other cancer phenotype, some other liver disease or some other disease which has not yet been analyzed.

It is unknown and unpredictable whether CLK1 is differentially expressed in patients having cancers other than liver cancer or having liver disorders other than liver cancer compared to healthy controls. Without this knowledge, it is not possible to conclude that differential expression of CLK1 in the blood of a test individual specifically indicates the presence of liver cancer, as claimed. A method for detection which relies on a comparison between expression in the blood of a test subject and control subjects requires the knowledge of this information in order to reliably "detect" liver cancer, as set forth in the claims. The instant specification has not established that all difference, no matter the magnitude nor the direction, relative to any control subjects or even relative to a healthy control subject is indicative of liver cancer. Furthermore, the specification has not shown that all expression at a level statistically the same as that observed in a population of patients having liver cancer is sufficient to conclude that liver cancer is present, as set forth in claim 55. In fact, it is unclear if this is a fair conclusion given the fact that CLK1 is also demonstrated to be differentially expressed in other phenotypes such as hyperlipidemia and rheumatoid arthritis. It is entirely unpredictable if this is also the case with other diseases. It is not known under what circumstances the result observed in the instantly examined control and test populations would be repeatable, as the results have not been

validated. All of these inquiries are particularly important in this case since the claims are silent as to which differential expression observations would be sufficient to detect the presence of liver cancer.

Further, the claims of the instant application set forth the comparison of the gene expression in a single individual versus as few as two other individuals, and they set forth that a comparing gene expression between the two is "indicative of" liver cancer. Neither the specification nor the claims set forth a threshold of difference between an individual's expression and the control samples expression of CLK1 in the blood that would be sufficient to conclude that the difference in gene expression between a test individual and any type control group is "indicative of" the recited liver cancer. Because the claims encompass any level of altered gene expression, it is relevant to point out that the art of Cheung et al (2003) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) (p.422, last paragraph; Fig 1). The data indicates that, for example, expression of ACTG2 in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3). It is thus unpredictable as to whether or not any level of altered gene expression is indicative of a liver cancer or the absence of liver cancer.

The unpredictability of correlating gene expression level to any phenotypic quality is taught in the post-filing art of Wu (2001). Wu teaches that gene expression data, such as microarray data, must be interpreted in the context of other biological knowledge, involving

various types of 'post genomics' informatics, including gene networks, gene pathways, and gene ontologies (p.53, left col.). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (p.63 - Discussion). The art of Newton et al (2001) further teaches the difficulty in applying gene expression results. Newton et al. teaches that a basic statistical problem is determining when the measured differential expression is likely to reflect a real biological shift in gene expression, and replication of data is critical to validation (p.38, third full paragraph). There is no replication of data in the instant specification.

Quantity of Experimentation

The instant specification does not provide enabling support for the practice of a single embodiment within the claimed invention since the claimed invention results in the detection of liver cancer. In particular, the specification does not provide adequate guidance to appraise one of ordinary skill in the art as to what levels of CLK1 gene expression must be observed to successfully conclude that liver cancer is present. Further, although the specification teaches there are differences in CLK1 levels in a liver cancer population versus a control patient population, and the specification teaches that for this population the difference is a 0.61 fold increase, the specification does not support the assertion in the claims that observing such an increase relative to any and all control populations of 2 or more individual is sufficient to "detect" liver cancer. Thus, given the lack of teaching in the specification and the highly

unpredictable nature of the technology, an extensive amount of work would be required to practice the claimed invention.

In order to practice the claimed invention, one would have to undertake an extensive amount of experimentation in a highly unpredictable technology area. One would have to begin by validating the results observed in the instant specification in a separate and larger population of healthy and liver cancer patients, in view of the established level of unpredictability in this technology area. One would have to further complete similar analysis for other diseases and conditions and control populations versus healthy controls and versus liver cancer controls in order to attempt to establish when and if analysis of CLK1 expression is sufficient to conclusively detect liver cancer. For example, consider the comparison of a test result and a control population of healthy individuals. If the test result is different from the level of expression observed in the healthy control group, does this mean liver cancer is present? How different from the average level of expression of healthy individuals would the test result have to be to indicate liver cancer- is a 0.61 fold difference required or a higher or lower threshold? Would any difference, up or down regulation be indicative of liver cancer? Or could one result indicate liver cancer and one a different disease such as hyperlipidemia or rheumatoid arthritis or cellular stress? Is CLK1 expressed in the blood of individuals with a disease other than those taught in the specification? Is this expression also diagnostic of other cancers, liver diseases or other disorders entirely unrelated to liver cancer? In order to reliably use a method for detecting liver cancer, one would first have to answer at least these questions. One would also, however, have to carry out this testing for validation, for it is possible that the result observed in the instant specification is intrinsic to the very small cohort of patients evaluated in applicant's study.

Further, one would have to undertake experimentation to determine difference thresholds required to determine that a patient has or does not have a disease.

As discussed, this art area is highly unpredictable.

Conclusion

The claims include methods which encompass the detection in blood of the expression of CLK1 in a test subject and comparing this expression to control subjects, wherein the comparison itself "is indicative of liver cancer." The identification of gene differential expression/disease indication relationships is a highly unpredictable endeavor, requiring extensive experimentation. The specification provides minimal guidance. In light of the factors discussed, therefore, it is concluded that it would require undue experimentation to practice the claimed invention.

Conclusion

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Thursday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is

(571)272-0507.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Juliet C. Switzer
Primary Examiner
Art Unit 1634

April 12, 2007